

Medicinal **Chemistry**



- Anti-neoplastic agents -

(Anti-Cancer agent) -

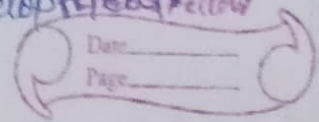
- * These are drugs used for the treatment of Cancer, malignancy, tumour, carcinoma, sarcoma, leukaemia & neoplasm.
- * Neoplasm \Rightarrow Group of diseases caused by several agents.
- * Cancer - It is characterized by an "abnormal" & "uncontrolled" cells division.
- * Cancer cells are two types \Rightarrow Primary ~~cell~~ tumour -
 \Rightarrow Secondary tumour (metastasis)
- * Oncology \Rightarrow Study of cancer cells.
- * Cell cycle kinetics -
 - Two key phase of cellular life-
 - a) DNA synthesis & mitosis to produce new cells.
 - b) Cell differentiation that produces specialized cells.

C.E. # Limitation of therapy - / treatment -

- Cancer cells very rapidly develop resistance to anti-neoplastic drugs.
- Anti-neoplastic agents kill cells by "first order kinetics"
- Anti-neoplastic agents kill a constant fraction of cells
- It is very difficult to kill all the malignant cells.
- Most anti-neoplastic drugs are highly toxic to the patients.

Adverse effects - Bone-marrow toxicity, Hair follicle toxicity, Hepato-toxicity, Skin rashes, Cardiac toxicity etc.

Bioliferation - The number of cells & size of cells ↑ essent
for body growth & development



* # Classification of anti-neoplastic drugs/agents -

- Based on drugs acting directly on cells (cyto-toxic drugs) -

(A) Alkylating agents -

- i. Nitrogen mustards - eg. - Mechlore-thamine*
 - Cyclo-phosphamide -
 - Chlorambucil -
 - melphalan -
- ii. Ethylenimine - eg. - Thiotepa -
- iii. Alkyl-sulfonate - eg. - Busulfan -

(B) Anti-metabolites -

- i. Purine antagonists - eg. - Mercapto-purine*
 - Thio-guanine -
 - Azathioprine -
- ii. Pyrimidine antagonists - eg. - Fluoro-uracil -
 - Cytarabine -
 - Flox-uridine -
- iii. Folate antagonists - eg. - metho-trexate* -

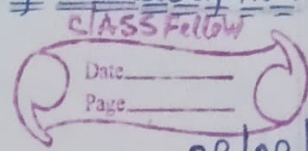
(C) Anti-biotics - eg. - D-actinomycin / Actinomycin-D - - Doxo-rubicin - - Doxo-rubicin - - Bleo-mycin -

(D) Plant-products -

- i. Micro-tubule damaging agents - eg. - Vinblastine sulphate
 - Vincristine sulphate
- ii. Topo-isomerase-2-inhibitors - eg. - Eto-poside -

• Alkylating agent affect \Rightarrow Replication & transcription -

- Adenine \Rightarrow N_1 & N_3 -
- Guanine \Rightarrow N_7 -
- Cytosine \Rightarrow N_3 -



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(E) Miscellaneous - eg. - Cisplatin -
- Mitotane -

Mechanisms of action of anti-neoplastic drugs -

(A) Alkylating agents \Rightarrow (are bifunctional), they have two alkylating group -

- Alkylating agents form covalent bond with particular nucleophilic substances in the cell



- Produce highly reactive carbonium ion intermediates



- Forms covalent bond with electron donors like - (amine, hydroxyl & sulf-hydroxyl groups)



- The nitrogen at position-7 (N_7) of guanine is probably the main molecular target for alkylation in DNA -



- They cause intra-chain / inter-chain cross-linking, abnormal base pairing -

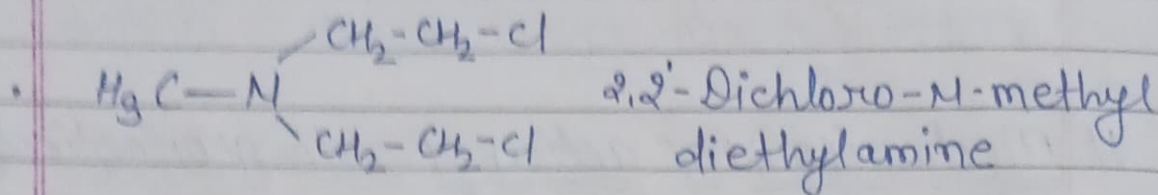


- Main impact is seen during replication of the DNA are unpaired (S-phase) -

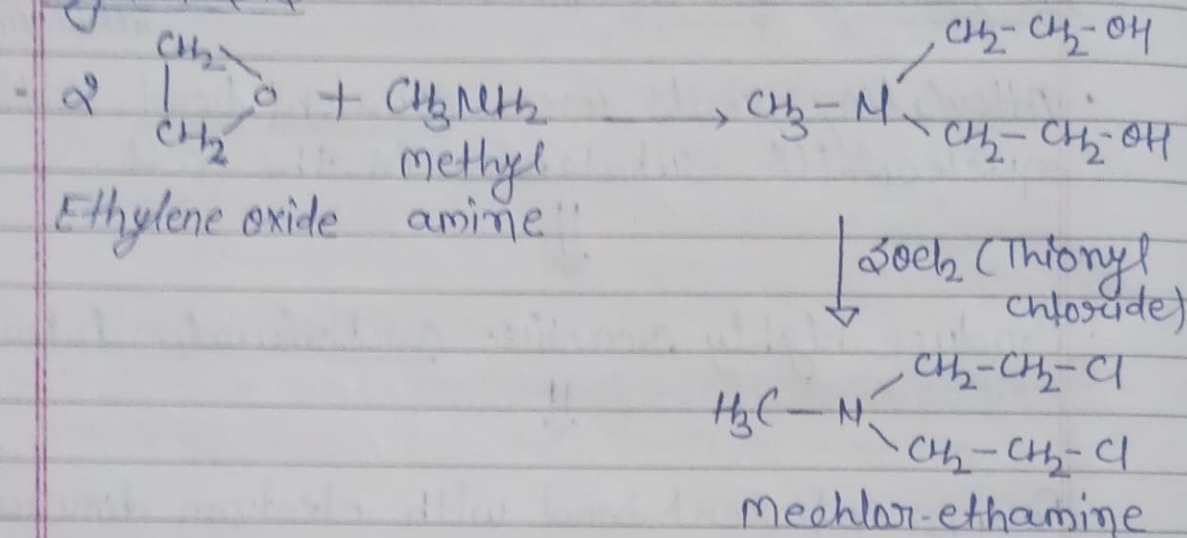


- Result in a block cell division & cell growth (G_2 -Phase) & apoptotic cell death -

eg. # Mechlor-Mechlor-ethamine* [Mustargen, Mustine].



• Synthesis -



• Uses -

- It is used in the treatment of "Hodgkin's disease".
- It is also used for the treatment of metastatic carcinoma.
- It is used topically in the treatment of "mycosis fungoides" (types of blood cancer) / T-cells lymphoma.

(B) Anti-metabolites -

• Metabolites are important constituent which are responsible for the DNA.
eg. - Purine, pyrimidine & folic acid which are used in the synthesis of DNA.

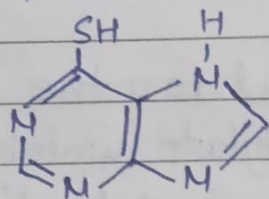
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* Anti-metabolites have similar structure as metabolites which prevent the biosynthesis of DNA-

⇒ Purin antagonist-

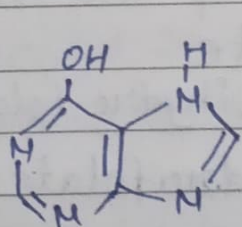
- 6-mercapto-purine (Pro-drugs)
- ⇓
- Converted in the cells to ribonucleotide of 6-mercapto-purine
- ⇓
- Suppresses/prevent de novo biosynthesis of purine
- ⇓
- No DNA synthesis -

eg. # 6-Mercaptopurine (Purinethol)

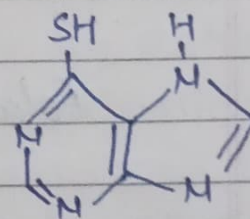
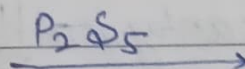


Purine-6-thiol

• Synthesis-



Purine-6-OH



6-mercapto-purine

• Uses-

- It is used in the treatment of acute monocytic leukaemia.-
- It is used as prevent the biosynthesis of purine-

ii) Pyrimidine antagonist -

- Deoxy uridine monophosphate (dUMP)
↓
- Inhibits thymidylate synthesis -
↓
- Blocks conversion of deoxy-uridylic acid to deoxy-thymidylic acid
↓
- Inhibition of DNA synthesis -

iii) Folate antagonist / Folic acid antagonist -

- Folates are essential for the synthesis of purine nucleotides & thymidylate which in turn are essential for DNA synthesis & cell division. -

• Folate

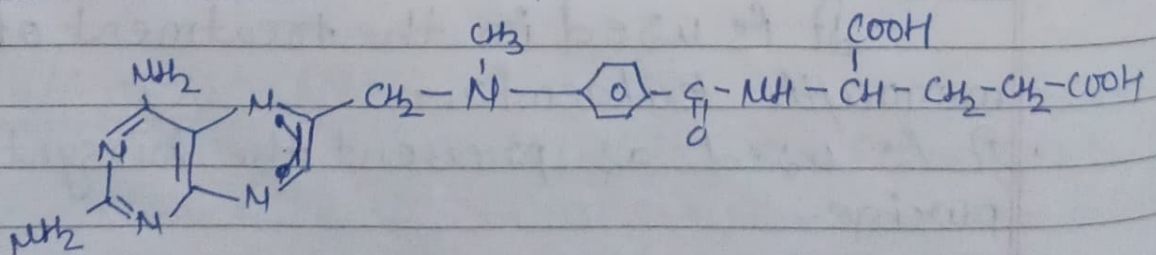
Folate antagonist → Dihydro-folate reductase

• Dihydro folate (FH_2) -

↓

• Tetra-hydro folate (FH_4)

eg. # Metho-trexate (Amehtopterin) -



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- Synthesis - Pyrimidine-2,4,5,6-tetra-amine
+
2,3-Dibromo propanal
↓ cyclisation
↓ dehydration
metho-trexate

• Uses -

• It is used for the treatment of acute lymphocytic leukaemia, acute lymphoblastic leukaemia, breast cancer, epidermoid cancer of the head, neck & lung cancer -

(C) Anti-biotics -

- Bind to DNA & inhibit both DNA & RNA synthesis
↓
- Produces breaks in DNA strands by activating topoisomerase-II & produces semi-quinone free radicals
↓
- Semi-quinone radicals reduce molecular oxygen to superoxide ions & H_2O_2
↓
- Single strand scission/cut of DNA -
↓
- No replication & cell division -

⑧ Plant products-

* Main veine alkaloids used in cancer chemotherapy-

• Inhibit mitosis -



• Bind to tubulin & inhibit its polymerisation into microtubules



• Preventing spindle formation in cell division



• Causing arrest/blocking at metaphase



• No replication & cell division-